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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,611	12/15/2005	Timo Flessner	LeA 36 225	6716

35969 7590 05/09/2008

Bayer Health Care LLC
400 Morgan Lane
West Haven, CT 06516

EXAMINER	
CHANDRAKUMAR, NIZAL S	
ART UNIT	PAPER NUMBER
1625	
MAIL DATE	DELIVERY MODE
05/09/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,611	FLESSNER ET AL.	
	Examiner	Art Unit	
	NIZAL S. CHANDRAKUMAR	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 13-16* is/are pending in the application.

4a) Of the above claim(s) *9,10 and 13-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/27/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-11, 13-16 are pending.

Election/Restrictions

Applicant's election without traverse of Group II, benzothiophene compounds, in the reply filed on 04/16/2008 is acknowledged.

Applicant did not identify the claims encompassing the elected invention as required in the office action filed 11/16/2007, page 4 , last but two line.

Claims 1-8 read on elected group of benzothiophene compounds.

Claims 9-11, 13-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 04/16/2008.

This application contains claims 9-11, 13-16 drawn to an invention nonelected with traverse in the reply filed on 04/16/2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 dependent claims rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

ClaimS 1-8 are drawn to solvates without defining what the chemical composition or structures of these solvates are. Solvates are defined in the art with chemical formulae such as (C8H6N2.HCl. 1.25 H2O). (The specification is replete with the term solvate, but no enabling disclosure of solvates is found in the specification. See below).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a limited class of compounds of the formula (I), does not reasonably provide enablement for the plurality of general structures as well as solvates claimed. The specification is enabling, for example, for making compounds of the formula (I) wherein the benzothiophene ring system is unsubstituted, that is for enabling disclosure with respect to making of the compounds is found for formula (I) wherein R3 = H, and benzene portion of the benzothiophene is unsubstituted except of the limitation of urea group. However R3 and the ring B of the formula are defined to include a variety of substituents. Further it is not seen where enablement is present in the specification for solvates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. As such, the specification does not enable any person skilled in the art to which it pertains, or with which is most nearly connected, to make the compounds of the invention commensurate in scope of these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: (1) breadth of the claims; (2) nature of the invention; (3) state of the prior art; (4) amount of direction provided by the inventor; (5) the level of predictability in the art; (6) the existence of working examples; (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure; and (8) relative skill in the art.

All of the factors have been considered with regard to the claim, with the most relevant factors discussed below:

The breadth of claims: The formula (I) encompasses several independently variable groups leading a large number of conceivable structures of widely different physical and chemical properties, characteristics that are art recognized to have major impact on the PK and PD properties. Further, the claims contain undefined compounds such as solvates rendering breadth of the claims wide.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the art of organic and medicinal chemistry, it is noted that each embodiment of the invention is required to be individually assessed for viability.

The amount of direction provided by the inventor and the presence or absence of working examples: The guidance and working examples provided in the specification is limited.

The methods for making amide bonds and urea formation are well-known to one of ordinary skill in the art. However, the preparation of substituted heterocyclic compounds needs special synthetic methods. Thus the disclosed methods on pages 21-23 for making the (un-substituted) benzothiophene carboxylic acid are not extendable to the preparation of the wide variety of substituted benzothiophenes claimed. This is because, the limitation, that is the requirement of the nitrogen functionality on the B ring, renders the disclosed methods unsuitable. The cited references on pages 21 (Bridges et al.) and on page 22 (Shiknova et al.) do not provide for the N-substitution on the B-ring. While the references

provide for halo substitution, nitro substations on the B-ring, it would require undue experimentation to convert these groups regioselectively, to the nitrogen substation for making urea moiety on the B-ring. In accordance with this, even though the applicant had possession of a R3 amino-substituted benzothiophene compound (see page 22), no use of this compound is disclosed in making compounds of formula (I) wherein R3 is amino.

The biological activity reported for the claimed compounds correspond to unsubstituted benzothiophenes.

It is not seen where in the specification enablement is present for thioureas.

It is not seen where in the specification enablement is present for R1 and R4 are other than H

It is not seen where in the specification enablement is present for R2 other than H.

The presence of azabicycle enables salt formation, however it is not seen where in the specification enabling disclosure is present for solvates.

The quantity of experimentation: In the instant case, there is a substantial gap between the compounds demonstrated and the breadth of the claims. Given that the enabling disclosure with respect to making the compounds is limited to unsubstituted benzothiophenes and the biological data reported is limited to unsubstituted benzothiophenes, in order to utilize the invention as claimed, the skilled artisan would be presented with an unpredictable amount of experimentation. Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to bridge this gap. The instant disclosure is broad and generic one that is not supported by the disclosure.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making solvates of the claimed compounds. The specification does not enable any person skilled in the art of synthetic organic chemistry to make the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized above. In the present

case the important factors leading to a conclusion of undue experimentation are the absence of any working example of a formed solvate, the lack of predictability in the art, and the broad scope of the claims. c) There is no working example of any hydrate or solvate formed. The claims are drawn to solvates, yet the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist.., the examples of the '881 patent do not produce the postulated compounds.., there is ... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly. g) The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid-State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it impossible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate. h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula (I) as well as the presently unknown list of solvents embraced by the term "solvate". Thus, the scope is broad. MPEP2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not

have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed.Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Amendments to limit the claims to the following

R2 = R3 = R4 = R5 = H,

B is unsubstituted benzo,

and deleting the terms 'solvates', would overcome the 112 first and second paragraph rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NIZAL S. CHANDRAKUMAR whose telephone number is (571)272-6202. The examiner can normally be reached on 8.30 AM - 4.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571 0272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nizal S. Chandrakumar

/D. Margaret Seaman/

Primary Examiner, Art Unit 1625